IOSR Journal Of Pharmacy
(e)-ISSN: 2250-3013, (p)-ISSN: 2319-4219
Volume 10, Issue 3 Series. I (March 2020), PP. 07-14
www.iosrphr.org

Constituents and pharmacology of *Onopordum acanthium*

Ali Esmail Al-Snafi
Department of Pharmacology, College of Medicine, Thi qar University, Iraq.
Received 01 March 2020; Accepted 16 March 2020

Abstract: Onopordum acanthium was used traditionally as bactericide, cardiotonic and hemostatic, diuretic, to treat nervousness, as antitumor agents and for the treatment of inflammation of the bladder and the respiratory and urinary systems. It contained saponins, alkaloids, sesquiterpen lactones, flavonoids, triterpenes, sterols, nitrogen-containing compounds, phenolic acids, coumarins, inulin, soluble sugars, proteins and oils. The pharmacological studies showed that Onopordum acanthium possessed antibacterial, antioxidant, anticancer, antiinflammatory, analgesic, antipyretic, hypotensive, antiepileptic, wound healing, xanthine oxidase and ACE inhibitory effects. The current review highlighted the chemical constituents, therapeutic and pharmacological effects of Onopordum acanthium.
Keywords: constituents, pharmacology, therapeutic effects, Onopordum acanthium

I. INTRODUCTION:

Plants produced secondary metabolites which represented an important source of pharmaceuticals, agrochemicals, flavours, fragrances, colours, biopesticides and food additives. Recent reviews showed that the medicinal plants possessed wide range of biological effects included central nervous, cardiovascular, antioxidant, endocrine and reproductive, gastro-intestinal, respiratory, antidiabetic, antimicrobial, antiparasitic, dermatological, anticancer, anti-inflammatory, antipyretic, analgesic, immunologicaland many other pharmacological effects[1-30]. *Onopordum acanthium* was used traditionally as bactericide, cardiotonic and hemostatic, diuretic, to treat nervousness, as antitumor agents and for the treatment of inflammation of the bladder and the respiratory and urinary systems. It contained saponins, alkaloids, sesquiterpen lactones, flavonoids, triterpenes, sterols, nitrogen-containing compounds, phenolic acids, coumarins, inulin, soluble sugars, proteins and oils. The pharmacological studies showed that *Onopordum acanthium* possessed antibacterial, antioxidant, anticancer, antiinflammatory, analgesic, antipyretic, hypotensive, antiepileptic, wound healing, xanthine oxidase and ACE inhibitory effects. The current review will highlight the chemical constituents, therapeutic and pharmacological effects of *Onopordum acanthium.*

Plant profile:
Synonyms:
Acanos spina, Acanthium onopordon, Carduus acanthium, Onopordum acanthium var. acanthium, Onopordum acanthium subsp. acanthium[31].

Taxonomic classification:
Kingdom: Plantae, **Subkingdom**: Viridiplantae, **Infrakingdom**: Streptophyta, **Superdivision**: Embryophyta, **Division**: Tracheophyta, **Subdivision**: Spermatophytina, **Class**: Magnoliopsida, **Superorder**: Asteranae, **Order**: Asterales, **Family**: Asteraceae, **Genus**: Onopordum, **Species**: *Onopordum acanthium*[32].
Common names:
Arabic: Toba, Eqsoon shawki, Ras alsheikh alshwki, shekai shawkiah, fis alhwmar, **English**: cotton thistle, giant thistle, heraldic thistle**,** Scotch thistle, Scottish thistle, woolly thistle,Scotch thistle; **French**: onoporde acanthi; **German**: gewöhnliche Eselsdistel; **Portuguese**: cardo-bastardo, cardo-espinhoso, cardo-selvagem; **Swedish**: ulltistel[33].

Distribution:
The plant is distributed in **Africa** (Algeria), **Asia** (Afghanistan, Iran, Iraq, Turkey, Armenia, Azerbaijan, Georgia, Russian Federation, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan, China, India, Pakistan), **Europe** (Austria, Czech Republic, Germany, Hungary, Netherlands, Slovakia, Switzerland, Belarus, Moldova, Ukraine, Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Greece, Italy, Macedonia, Montenegro, Romania, Serbia, Slovenia, France, Portugal, Spain, Estonia, Latvia, Lithuania, Denmark, Norway, Sweden, United Kingdom, Belgium, Poland, France),

Australasia (Australia, New Zealand), **Northern America** (Canada, United States) and **Southern America** (Argentina, Chile, Uruguay)[33].

Description:

is a biennial herb that grows to 50–200 cm in height. Stem erect, usually branched above, stout, glabrous or cobwebby; wings 2-5 cm wide, with triangular spiny lobes or teeth; spines yellowish brown, to 5 mm. Leaves have stout yellow spines on the edge and thick pubescence. Middle and upper cauline leaves sessile, narrowly elliptic to oblanceolate, gradually smaller upward. Capitula solitary. Involucre globose to ovoid, ca. 5 cm in diam., cobwebby, glabrescent. Phyllaries abaxially gland-dotted, margin ciliate; outer and middle phyllaries ovate-subulate to lanceolate-subulate, 1.7-1.8 × 0.4-0.5cm, leathery, apex narrowed into a pungent divaricate to reflexed spine; inner phyllaries lanceolate to linear, 2-3 × ca. 0.3 cm, straight, apex acuminate-subulate. Corolla purplish red to pink, ca. 2.4 cm, tube ca. 1.2 cm. Achene grayish black to gray, obovoid to narrowly ellipsoid, ca. 6 mm, 3-ribbed, transversely wrinkled, apical rim not prominent[34].

Traditional uses:

Seed oil was used for burning and cooking[35]. *Onopordum acanthium* was used in Europe as an edible plant[36]. In Bulgarian folk medicine, the plant was used as refreshing and invigorating[37]. *Onopordum acanthium* was also used as bactericide, cardiotonic and hemostatic and for the treatment of hypotonicity; ripe seeds were used for heart diseases, poor blood circulation, as bactericidal, as hemostatic, diuretic, to treat nervousness and as antitumor agents. Aqueous extract of *Onopordum acanthium*, was used in Jordan traditional medicine in the treatment of various type of cancer. The plant was also used to diminish discharges of mucous membranes, and topically for skin cancer. The infusion of leaves and inflorescences was used to decreases edema of various origins[38-40].

Inflorescences, roots, seeds, and late developing leaves of *Onopordum acanthium* were used internally in the traditional medicine of Central Asia for the treatment of inflammation of the bladder and the respiratory and urinary systems[41].

Parts used:

The flowering plant, the juice, seeds and roots[38-41].

Chemical constituents:

The preliminary phytochemical analysis showed that the plant contained saponins, alkaloids, sesquiterpen lactones, flavonoids, triterpenes, sterols, lipids, nitrogen-containing compounds, phenolic acids, coumarins, inulin, soluble sugars(10.35 ± 0.54%), protein (14.9 ± 0.51%) and oil (14.36 ± 0.56%). Fatty acids identified in the plant were palmitic (8.81) stearic (4.43) oleic (28.79), and linoleic(57.65) (% of the total fatty acids) [38, 42].

Fatty acid composition of *Onopordum acanthium* seed oils from Bulgaria was: lauricoleic 11, myristic 2, miristicoleic 19, palmitic 99, palmitoleic 1, margaric 1, stearic 9, oleic 342, linoleic 511, arachidic 1, gadoleic 1and behenic 3 g/kg. Sterol composition of seed oils: cholesterol 11, brassisterol 16, campesterol 128, Δ7-campesterol 48, stigmasterol 33, β-sitosterol 632, Δ^5-avenasterol 36, Δ^7-stigmasterol 57 and Δ^7-avenasterol 39 g/kg. Phospoholipid composition of seed oils: phosphatidylcholine 183, phosphatidyl ethanolamine188, phosphatidylinositol 320, phosphatidic acids 147 and diphosphatidyl glycerol 162 g/kg. While, tocopherol composition of seed oils: α - tocopherol 911 and α - tocotrienol 89 g/kg[43].

Nine fatty acids and six phytosterols were identified in Tunisian *Onopordum acanthium* seeds during ripening. The main fatty acids were linoleic acid (0.18-8.06 mg/g of seed), oleic acid (0.051-2.45 mg/g of seed), palmitic acid and stearic acid. Pentadecanoic acid was in unripe fruits, while, the two last stages of development were characterised by a relative abundance of erucic acid. β-sitosterol (34.5-77.79% of total sterols) was the major 4-desmethylsterols during maturation. The first episodes of growth were characterized by the best amounts of stigmasterol and campesterol, while stigmastanol and Δ^7 sitosterol were abundant in the semi-ripe and fully ripe fruits[44]; *Onopordum acanthium* contained germacranes (onopordopicrin, arctiopicrin)[45-47]; guaianolide sesquiterpenes (4β,14-dihydro-3- dehydrozaluzanin C, zaluzanin C and 4β,15,11β,13- tetrahydrozaluzanin C)[38, 48]; lignin ([(+)-pinoresinol, syringaresinol, medioresinol)[49]; flavonoids (apigenin, luteolin, chrysoeriol, quercetin, eridictyol, nepetin, nepetin, apigenin 7-O-glucoside, apigenin 7-O-rutinoside, apigenin 7-O-β-D-glucuronide, luteolin-7-glucoside, quercetin-3-O-glucoside, isorhamnetin-3-O-glycoside, cyanidin-3,5-diglucoside)[46, 50]; steroids and triterpenes (Δ^5-avenasterol, campesterol, stigmasterol, ß-sitosterol, brassicasterol, cholesterol, lupeol, lupeol acetate, taraxasterol, taraxasteryl acetate, α-amyrin, α-amyrin acetate)[51-52]; and many other constituents included (caffeic acid, succinic acid, chlorogenic acid, aconiside, aesculin, 1-amino-2-propanol, alanine, leucine, valine, proline, ϒ-aminobutyric acid, stachydrine, choline)[50, 53-55].

Arctiin and isochlorogenic acid were isolated from the methanol extract of the *Onopordum acanthium* fruit (38.0 ± 3.2 mg/g and 3.5 ±0.4 mg/g fruits) and paraffins in the n-hexane extract (195.6 ± 5.6 mg/g fruits)[56].

Lignans (pinoresinol, syringaresinol, and medioresinol) and flavonoids (hispidulin, nepetin, apigenin, and luteolin) were isolated from the chloroform soluble part of the methanol extract of the aerial parts of *Onopordum acanthium*. While, (4β,15-dihydro-3-dehydrozaluzanin C, zaluzanin C, 4β,15,11β,13-tetrahydrozaluzanin C, nitidanin diisovalerianate, 24-methylenecholesterol, and 13-oxo-9Z,11E-octadecadienoic acid) were isolated from *Onopordum acanthium* root[57].

The total phenolic content of the butanolic extract of *Onopordum acanthium* was 8.93 ± 0.133 mg gallic acid/100 mg dry extract and flavonoid content was 3.93± 0.037 mg catechin/100 mg dried extract[58].

The total phenolic and flavonoid contents were determine in methanol, ethanol, and acetone extracts from flowers and leaves of *Onopordum acanthium*. The total phenolic contents of ethanolic, methanolic and acetone flower extracts were 19.71, 24.70 and 13.94 mg GAE/l, while, the phenolic contents in the same extracts of the leaves were 26.34, 30.47 and 36.67 mg GAE/l respectively. The total flavonoid contents in the ethanolic, methanolic and acetone flower extracts were 30.37, 42.09 and 32.40 mg QE/l, and the total flavonoid contents in the same extracts of the leaves were 40.06, 53.18 and 85.37 mg QE/l[59].

Pharmacological effects:

Antibacterial effect:

The antibacterial properties of n-hexane and methanol extracts of *Onopordum acanthium* seeds were screened against Gram-positive (*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Micrococcus loteus*) and Gram-negative bacteria (*Escherichia coli* and *Klebsiella pneumonia*). Methanol extract showed significant antibacterial activity against Gram-positive bacteria; *Staphylococcus epidermidis* and *Micrococcus luteus* (with MIC= 0.612 mg/ml), while methanol and n-hexane showed no inhibitory activity against Gram-negative bacteria[60].

The antibacterial effect of *Onopordum acanthium* leaf extract was investigated against eight bacterial strains including two plant and three human pathogens and a soil, a marine and a probiotic human gut bacteria, with identification of antibacterial active compounds. HPLC-MS/MS analysis resulted in identification of three active antibacterial compounds, linoleic, linolenic acid and germacranolide sesquiterpene lactone (onopordopicrin)[61].

Anticancer effect:

Sesquiterpene lactones isolated from *Onopordum acanthium* were tested for antiproliferative action on HL-60 leukemia cells, they were exhibited IC_{50} values in the range of 3.6-13.5 μM. They caused cell cycle disturbance characterized by increases in the G1 and G2/M populations, with a decrease in the S phase. They elicited concentration- dependent chromatin condensation and disruption of the membrane integrity. They also significantly increased the activity of caspases-3 and -9, indicating that sesquiterpenes induced the mitochondrial pathway of apoptosis[62].

Crude hydromethanolic (80% methanol) extracts of *Onopordum acanthium* leaves and *Spartium junceum* flowers were tested for cytotoxic effects against glioblastoma U-373 tumour cells. *Onopordum acanthium* extract was ~5 times more cytotoxic than *Spartium junceum* extract (IC_{50} values 309 and 1602μg/ml, respectively). *Onopordum acanthium* extract killed the cells via apoptosis, which was confirmed by the activation of caspase-3[63].

Antiproliferative activities (%) of *Onopordum acanthium* (flowers/fruits) n-hexane fraction of aqueous methanolic extract were against HeLa (cervix adenocarcinoma), MCF7 (breastadenocarcinoma) and A431 (skin epidermoid carcinoma) were 13.07± 3.13, 9.12± 4.29, 12.40± 1.21% respectively, while antiproliferative activities of chloroform fraction of aqueous methanolic extract were 29.82± 1.35, 24.30± 1.07, 29.93± 3.64%, the antiproliferative activities of aqueous methanolic extract were 43.70± 2.0, 14.05± 2.3, 25.24± 3.04%, and antiproliferative activities of the aqueous extract were 75.40± 2.6, 57.13± 2.24, −1.43± 1.46% against the same cell line, respectively[64].

The cytotoxic effect of methanolic, butanol, chloroform and petroleum ether extracts of *Onopordum acanthium* was studied using brine shrimp lethality bioassay. Methanolic, chloroform, petroleum ether extract showed LC_{50} value more than 500 μg/ml whereas butanolic extract had LC_{50} less than 500 μg/ml[58].

The cytotoxic effects of total methanol extract and petroleum ether, chloroform and methanol fractions of eighteen plants collected from Ardebil-Iran, were investigated against 4 selected human cancer cell lines (MCF7, HepG-2, A-549, HT-29) and a normal cell line. Total methanol extract and chloroform fraction of the aerial parts of *Onopordon acanthium* showed significant cytotoxic effect against all cell lines with (IC_{50} 12.51 to 55.72 and (IC_{50} 6.49 to 31.5), respectively[65].

The antiproliferative activities of six compounds isolated from *Onopordum acanthium* (4β,14-dihydro-3-dehydrozaluzanin C, zaluzanin C, 4β,15,11β,13-tetrahydrozaluzanin C, nitidanin-diisovalerianate, 13-oxo-9*Z*,11*E*-octadecadienoic acid and 24-methylenecholesterol) were studied against cervix adenocarcinoma HeLa, breast adenocarcinoma MCF7 and skin epidermoid carcinoma A431 cells. It 4β,14-dihydro-3-dehydrozaluzanin C, was the most active antiproliferative compound, it exerted remarkable tumor cell growth inhibitory activity (IC_{50}: 2.7–15.1 μM)[48].

Thirteen aqueous extracts of Jordanian plants were tested in mice for their ability to augment natural killer (NK) cell function *in vitro* in generating cytotoxicity against YAC tumor targets. Maximum NK augmentation (38.3%) was recorded at 1:50 dilution of the aqueous extracts of *Onopordum acanthium*[66]. The same plant extracts induced significant enhancement of of NK cell activity against K562 tumor cells. This increase in NK cell cytotoxicity was due to the enhancement of NK cell production of interferon-γ, and tumor necrosis factor-α (60–200%). They also significantly increased the release of granzyme A and nacetyl-β-D-glucosaminidase. In addition, with the absence of IL–2, the extracts caused significant increase in NK-cell-induced cytotoxicity against K562 tumor cells, and in the presence of IL2 stimulated cells, the plant extracts caused an increase in NK cell cytotoxicity[67].

Antiinflammatory, analgesic and antipyretic effects:

The anti-inflammatory effect butanolic extract of *Onopordum acanthium* was studied using carrageenan-induced paw edema model in rats. Butanolic extract 200 and 400 mg/kg bw decreased the edema by 37.78 % and 40.52 %, respectively; standard aspirin 100 mg/kg decreased edema by 42.62 % at 5th hour of carrageenan injection[58].

The anti-inflammatory effects of *Onopordum acanthium* extracts and many isolated compounds were investigated by determine their inhibitory effect on nuclear factor kappa B1 gene expression, nitric oxide production, leukotriene biosynthesis (5-lipoxygenase), and cyclooxygenase-1 and cyclooxygenase-2 enzymes. *Onopordum acanthium* extracts exerted strong inhibitory activities on *in vitro*. 4β,15-Dihydro-3-dehydrozaluzanin C and zaluzanin C at 20 μM were the most active constituents against lipopolysaccharide/interferon-γ-induced nitric oxide production (100.4 ± 0.5% and 99.4 ± 0.8%), caused inhibition of cyclooxygenase-2 (98.6 ± 0.2% and 97.0 ± 1.1%) and nuclear factor kappa B1 gene expression (76.7 ± 7.3% and 69.9 ± 3.4%). However, it appeared that these inhibitory effects were not due to cytotoxicity of the tested compounds[58].

The anti-inflammatory activity (IL-8 and E-selectin) of *Onopordum acanthium* was investigated in HUVECtert cells stimulated with TNF-alpha and LPS. Dose dependent (from 15 to 40 microg ME/ml corresponding to 20-75 micro M arctiin) inhibition of E-selectin and of the induction of IL-8 were recorded[56].

The extracts of *Onopordum acanthium* were evaluated for their inhibitory activity on COX-2 and NF-κB1 gene expression, inducible nitric oxide synthase (iNOS), 5-LOX, and COX-1 and COX-2 enzymes at 10 or 50 μg/ml *in vitro*. In most cases, the chloroform extract exerted strong inhibitory effects [inhibition of iNOS (76.7 ± 7.0%), 5-LOX (62.6 ± 6.8%), and inhibition of COX-2 enzyme (61.8 ± 9.0%)][49].

Seven compounds [(+)-pinoresinol, (+)-syringaresinol, medioresinol, hispidulin, nepetin, nepetin, luteolin and apigenin] isolated from the active chloroform extract of the aerial parts of the plant were tested at 20 μM for their inhibitory effects on COX-2 and NF-κB1 gene expression, iNOS, 5-LOX, COX-1 and COX-2 enzymes *in vitro*. Among the flavonoids, luteolin was the most potent compound, markedly inhibiting the biosynthesis of leukotriene (74.6 ± 8.8%) and exhibiting moderate inhibitory activity on COX-2, NF-κB1 gene expression, and iNOS[49].

The analgesic and antipyretic activities of butanolic extract of *Onopordum acanthium* were studied using 20 % brew yeast injection induced pyretic model, and 1 % acetic acid induced analgesic model in rats. Butanolic extract 200 and 400 mg/kg significantly decreased acetic acid-induced abdominal writhes compared to standard aspirin. Butanolic extract also showed dose and time dependent decrease in body temperature in yeast induced pyrexia, comparable to standard, aspirin[58].

Xanthine oxidase inhibitory effect:

The xanthine oxidase inhibitory effect of *Onopordum acanthium* was studied *in vitro*. *Onopordum acanthium* extracts possessed weak xanthine oxidase inhibition (IC_{50} 572.9 μg/ml)[58].

ACE inhibition and hypotensive effect:

The angiotensin converting enzyme (ACE) inhibition activity of [(*E*)-1-oxo-3,4-dihydro-1*H*-isochromen-7-yl-3-(3,4-dihydroxyphenyl) acrylate] isolated from *Onopordon acanthium*, was determined using hippuryl-L-histidyl-L-leucine (HHL) as substrate in an *in vitro* ACE assay. The isolated compound possessed 83±1% ACE inhibition activity at concentration of 330 μg/ml[68].

The ACE inhibitory activity of *Onopordon acanthium* was evaluated by determining the hydrolysis rate of (HHL) substrate, using reverse phase high performance liquid chromatography (RP-HPLC). *Onopordon acanthium* extract possessed > 50% ACE inhibition activity at 330 µg/ml concentration[(69)].

A clinical trial was performed to determine the antihypertensive effects of *Onopordon acanthium* (2 capsules, each contained 1g of *Onopordon acanthium* seed extract as add-on therapy, two times per day) in patients receiving 50 mg losartan. *Onopordon acanthium* seed extract possessed hypotensive effects, it significantly reduced SBP and DBP at the end of 8 weeks[(70)].

Antioxidant effect:

The antioxidant activity of a compound isolated from *Onopordon acanthium*, was measured using DPPH radical scavenging assay. The isolated compound possessed acceptable antioxidant activity (IC_{50} value of 2.6±0.04 µg/ml) in comparison with BHT (IC_{50} value of 10.3±0.15 µg/ml) and Trolox (IC_{50} value of 3.2±0.06 µg/ml)[(71)].

The antioxidant effect of butanolic extract of *Onopordum acanthium* was studied using DPPH-assay. Strong antioxidant activity was possessed by the butamol extract, IC_{50} = 134.4 µg/ml with considerable amount of total phenolic (8.93 ± 0.133 mg gallic acid/100mg dry extract) and flavonoid content (3.93± 0.037 mg catechin/100 mg dry extract)[(58)].

The free radical scavenging activity of methanol, ethanol, and acetone extracts from flowers and leaves of *Onopordum acanthium* were assayed by DPPH radical scavenging method, and the effects of extracts on CAT, GST, and GPx enzyme activities were also investigated. *Onopordum acanthium*, possessed antioxidant and free radical scavenging activity with potential to inhibit GPx and GST enzymes[(59)].

20% ethanol and hydromodule (solid: liquid) 1:10 extract produced the highest antioxidant capacity, which positively correlated with the polyphenolic content[(72)].

Antiepileptic effect:

The antiepileptic effect of *Onopordon acanthium* secondary metabolite (onopordia) (0.1, 1 and 10 mg/kg, ip, 30, 60 and 120 min prior to induction of epileptic seizure), was investigated in pentylenetetrazole (PTZ)-induced seizure in male mice with the investigation of possible role of nitric oxide pathway. Onopordia possessed anticonvulsant effects when administrated at dose of 10 mg/kg, ip and the optimum time was 60 min prior to induction of seizure. Anticonvulsant effect of onopordia was blocked by applying a single dose of a non-selective nitric oxide synthase (NOS) inhibitor, Nω-nitro-L-arginine methyl ester hydrochloride (10 mg/kg, ip), and also a single dose of a selective neuronal NOS inhibitor, 7-nitroindazole (30 mg/kg, ip). Administration of ketamine as a N-Methyl-D-aspartic acid receptor antagonist (0.5 mg/kg; ip) with onopordia did not change the anticonvulsant effect of onopordia. The results indicated that the antiepileptic effect of onopordia was attributed to NO/nNOS pathway on PTZ-induced seizure in mice[(73)].

Wound healing effect:

The hydroalcoholic extract of the roots, stems, leaves and flowers were formulated into an eucerin-based ointment and applied once daily to a full thickness excision wound (2x2 cm) inflicted on the mid-dorsal area of white New Zealand rabbit. The results showed that the hydroalcoholic extract of the flowers was the most effective. Dose-response curves showed that 0.2% w/w flowers extract was the optimum concentration which induced fastest rate of healing (complete healing in 6 days compared with 17 days with the ointment base alone)[(74)].

II. CONCLUSION

The current review discussed the chemical constituents, pharmacological effects and therapeutic importance of *Onopordum acanthium* as a promising medicinal plant with wide range of pharmacological activities which could be utilized in several medical applications because of its effectiveness and safety.

REFERENCES:

[1]. Al-Snafi AE. Chemical constituents and pharmacological activities of *Lantana camara*- A review. Asian J Pharm Clin Res 2019; 12912):10-20.
[2]. Al-Snafi AE. Chemical constituents and pharmacological effects of *Lepidium sativum*- A review. International Journal of Current Pharmaceutical Research 2019; 11(6):1-10.
[3]. Al-Snafi AE. Constituents and pharmacology of *Fumaria officinalis*- A review. IOSR Journal of Pharmacy 2020; 10(1):17-25.
[4]. Al-Snafi AE. Chemical constituents and pharmacological effects of *Melilotus Officinalis*- A review. IOSR Journal of Pharmacy 2020; 10(1):26-36.

[5]. Al-Snafi AE. Bioactive metabolites and pharmacology of *Cistanche tubulosa*- A review. IOSR Journal of Pharmacy 2020; 10(1): 37-46.
[6]. Al-Snafi AE. The Pharmacological importance of *Bauhinia variegata*. A Review. Journal of Pharma Sciences and Research 2013; 4(12): 160-164.
[7]. Al-Snafi AE. The medical benefit of *Gnaphalium luteoalbum*-A review. IOSR Journal of pharmacy 2019; 9(5): 40-44.
[8]. Al-Snafi AE. Chemical constituents and pharmacological effects of *Lythrum salicaria* - A review. IOSR Journal of Pharmacy 2019; 9(6): 51-59.
[9]. Al-Snafi AE. Medical benefit of *Malva neglecta* - A review. IOSR Journal of Pharmacy 2019; 9(6): 60-67.
[10]. Al-Snafi AE. A review on *Lagerstroemia indica*: A potential medicinal plant. IOSR Journal of Pharmacy 2019; 9(6): 36-42.
[11]. Al-Snafi AE. Pharmacological and Therapeutic effects of *Lallemantia royleana*- A review. IOSR Journal of Pharmacy 2019; 9(6):43-50.
[12]. Al-Snafi AE. Chemical constituents and pharmacological effects of *Lathyrus sativus*- A review. IOSR Journal of Pharmacy 2019; 9(6): 51-58.
[13]. Al-Snai AE. Iraqi medicinal plants with antifungal effect- A review. IOSR Journal of Pharmacy 2019; 9(7): 16-56.
[14]. Al-Snai AE. Iraqi medicinal plants with antiviral effect- A review. IOSR Journal of Pharmacy 2019; 9(7): 57-75.
[15]. Al-Snai AE. A review on *Lycopus europaeus*: A potential medicinal plant. IOSR Journal of Pharmacy 2019; 9(7): 80-88.
[16]. Al-Snai AE. *Lemna minor*: Traditional uses, chemical constituents and pharmacological effects- A review. IOSR Journal of Pharmacy 2019; 9(8): 6-11.
[17]. Al-Snai AE. Chemical constituents and pharmacological effects of *Lithospermum officinale*. IOSR Journal of Pharmacy 2019; 9(8): 12-21.
[18]. Al-Snai AE. Iraqi medicinal plants with antibacterial effect- A review. IOSR Journal of Pharmacy 2019; 9(8): 22-103.
[19]. Al-Snai AE, Talab TA. A review of medicinal plants with nephroprotective effects. GSC Biological and Pharmaceutical Sciences 2019; 8(1): 114-122.
[20]. Al-Snai AE, Al-Kamel ML, Esmael ME. Antifungal effect of *Alhagi maurorum* phenolic extract. IOSR Journal of Pharmacy 2019; 9(8): 7-14.
[21]. Al-Snai AE. Pharmacological and therapeutic effects of *Lippia nodiflora* (*Phyla nodiflora*). IOSR Journal of Pharmacy 2019; 9(8):15-25.
[22]. Al-Snai AE, Mousa HM, Majid WJ. Medicinal plants possessed hepatoprotective activity. IOSR Journal of Pharmacy 2019; 9(8): 26-56.
[23]. Al-Snafi AE. Medical benefit of *Lallemantia iberica*- A review. To Chemistry Journal 2019; 3: 97-102.
[24]. Al-Snafi AE. Constituents and pharmacological effects of *Leontice leontopetalum*- A review. To Chemistry Journal 2019; 3: 103-108.
[25]. Al-Kamel ML and Al-Snafi AE. Antibacterial effect of the phenolic extract of *Alhagi maurorum*. IOSR Journal of Pharmacy 2019; 9(9):47-55.
[26]. Al-Snafi AE. A review on *Luffa acutangula*: A potential medicinal plant. IOSR Journal of Pharmacy 2019; 9(9):56-67.
[27]. Al-Snafi AE. Constituents and pharmacology of *Luffa cylindrica*- A review. IOSR Journal of Pharmacy 2019; 9(9):68-79.
[28]. Al-Snafi AE. A review on *Lawsonia inermis*: A potential medicinal plant. International Journal of Current Pharmaceutical Research 2019; 11(5):1-13.
[29]. Al-Snafi AE. Medicinal value of *Lagerstroemia speciosa*: An updated review. International Journal of Current Pharmaceutical Research 2019; 11(5):18-26.
[30]. Salehi B, Krochmal-Marczak B, Skiba D, Patra JK, Das SK Das G, Popović- Djordjević JB, Kostić AZ, Kumar NV, Tripathi A, Al-Snafi AE, Arserim-Uçar DK, Konovalov DA, Csupor D, Shukla I, Azmi L, Mishra AP, Sharifi-Rad J, Sawicka B, Martins N, Taheri Y, Fokou BVT, Capasso R and Martorell M. *Convolvulus* plant- A comprehensive review from phytochemical composition to pharmacy. Phytotherapy Research 2019;1–14.
[31]. The plant list, *Onopordum acanthium*, http://www.theplantlist. org/tpl1.1/ record/ gcc-90654
[32]. ITIS, *Onopordum acanthium*, https://www.itis.gov/servlet/ SingleRpt/ Single Rpt? search_topic=TSN&search_value=38140
[33]. U.S. National Plant Germplasm System, *Onopordum acanthium*, https://npgsweb. ars-grin.gov/gringlobal/taxonomydetail.aspx?104466

[34]. Flora of China, *Onopordum acanthium*, http://www.efloras.org/florataxon. aspx? flora_id=2&taxon_id=200024335
[35]. Grieve M. A modern herbal: The Medicinal Culinary Cosmetic and Economic Properties Cultivation and Folk-lore of Herbs, Grasses, Fungi, Shrubs & Trees with All Their Modern Scientific Uses, V. 1, Dover Publication, New York, 1971: 888.
[36]. Lim TK. Edible medicinal and non-medicinal plants. Springer- Dordrecht, Netherlands, 2014: V.7.
[37]. Petkov V. Modern phytotherapy. State Publishing House. Medicina i fizkultura. Sofia, 1982:513.
[38]. Bruno M, Maggio A, Rosselli S, Safder M and Bancheva S. The metabolites of the genus *Onopordum* (Asteraceae): Chemistry and biological properties. Current Organic Chemistry 2011; 15: 888-927.
[39]. Mobli M, Qaraaty M, Amin G, Haririan I, Hajimahmoodi M and Rahimi R. Scientific evaluation of medicinal plants used for the treatment of abnormal uterine bleeding by Avicenna. Arch Gynecol Obstet 2015; 292: 21-35.
[40]. Mamedov NA, Mehdiyeva NP and Crake LE. Medicinal plants used in traditional medicine of the Caucasus and North America. J Med Active Plants 2015; 4: 42–66.
[41]. Eisenman SW, Zaurov DE and Struwe L. Medicinal Plants of Central Asia: Uzbekistan and Kyrgyzstan. New York: Springer, 2013: 178.
[42]. Tonguc M and Erbas S. Evaluation of fatty acid compositions and some seed characters of common wild plant species of Turkey. Turk J Agric Forestry 2012; 36: 673-679.
[43]. Zhelev I, Merdzhanov P, Angelova-Romova M, Zlatanov M, Antova G, Dimitrova-DyulgerovaI and Stoyanova A. Lipid composition of *Carduus thoermeri* Weinm, *Onopordum acanthium* L. and *Silybum marianum* L., growing in Bulgaria. Bulgarian Journal of Agricultural Science 2014; 20(3):622-627.
[44]. Arfaoui MO, Renaud J, Ghazghazi H, Boukhchina S and Mayer P. Variation in oil content, fatty acid and phytosterols profile of *Onopordum acanthium* L. during seed development. Nat Prod Res 2014;28(24):2293-2300.
[45]. Drozdz B, Holub M, Samek Z, Herout V and Sorm F. The constitution and absolute configuration of onopordopicrine- a sesquiterpene lactone from *Onopordon acanthium* L. Collect Czech Chem Commun 1968; 33: 1730-1737.
[46]. Karl C, Mueller G and Pedersen PA. Zur Phytochemie der Blüten von *Onopordon acanthium* L. (Eselsdistel). Deutsche Apoth Zeit 1976; 116: 57-59.
[47]. Bogs HU and Bogs U. Constituents of *Onopordum acanthium*. I. Coumarins and flavones. Pharmazie 1965; 20: 706-709.
[48]. Csupor-Löffler B, Zupkó I, Molnár J, Forgo P and Hohmann J. Bioactivity guided isolation of antiproliferative compounds from the roots of *Onopordum acanthium*. Nat Prod Commun 2014; 9: 337–340.
[49]. Lajter I. Biologically active secondary metabolites from Asteraceae and Polygonaceae species, PhD Thesis, Szeged- Hungary, 2015.
[50]. Bogs HU and Bogs U. Über die Inhaltsstoffe von *Onopordon acanthium* L. Pharmazie 1967;22: 54-58.
[51]. Nolasco SN, Bertoni MH, Malec L and Cattaneo YP. Seeds of *Onopordon acanthium* L. (Scotch thistle), *Carduus acanthoides* L. (plumeless thistle) and *Cirsium vulgare* (Savi) Ten (bull thistle). Extracted crude oils and seed meals. An Asoc Quim Argent 1987;75:29-34.
[52]. Khalilova AZ, Shakurova ER, Nuriev IF, Akhmetova VR, Khalilov LM and Dzhemilev UM. Triterpenoids of *Onopordum acanthium* (Asteraceae). Rastitel'nye Resursy 2007;43(1):97-102.
[53]. Karl C, Mueller G and Pedersen PA. Zur Phytochemie der Blüten von *Onopordon acanthium* L. (Eselsdistel). Deutsche Apoth Zeit 1976; 116: 57-59.
[54]. Bohlmann F, Kohn S and Waldau E. Der Poyine des Subtribus Carduinae. Chem Ber 1966; 99:3201-3203.
[55]. Tyunkina TV, Nuriev IF, Khalilov LM, Akmetova VR and Dzhemilev UM. PMR and 13C NMR spectra of biologically active compounds. XIII. Structure and stereochemistry of a new phenylpropanoid glycoside isolated from *Onopordon acanthium* seeds. Chem Nat Comp 2009; 45:61-65.
[56]. Daci A, Gold-Binder M, Garzon D, Patea A and Beretta G. Standardization of solvent extracts from *Onopordum acanthium* fruits by GC-MS, HPLC-UV/DAD, HPLC-TQMS and 1H-NMR and evaluation of their inhibitory effects on the expression of IL-8 and E-selectin in immortalized endothelial cells (HUVECtert). Nat Prod Commun 2014;9(7):945-948.
[57]. Lajter I, Pan SP, Nikles S, Ortmann S, Vasas A, Csupor-Löffler B, Forgó P, Hohmann J and Bauer R. Inhibition of COX-2 and NF-κB1 gene expression, NO production, 5-LOX, and COX-1 and COX-2 enzymes by extracts and constituents of *Onopordum acanthium*. Planta Med 2015;81(14):1270-1276.
[58]. Habibatni S, Zohra AF, Hani K, Anwar S, mansiI and Ali NAA. *In vitro* antioxidant, xanthine oxidase-inhibitory and *in vivo* anti-inflammatory and analgesic, antipyretic activity of *Onopordum acanthium*. International Journal of Phytomedicine 2017; 9:92-100.

[59]. Koc S, Isgor BS, Isgor YG, Moghaddam NS and Yildirim O. The potential medicinal value of plants from Asteraceae family with antioxidant defense enzymes as biological targets. Pharm Biol 2015; 53(5): 746–751.
[60]. Zare K, Nazemyeh H, Lotfipour F, Farabi S, Ghiamirad M and Barzegari A. Antibacterial activity and total phenolic content of the *Onopordon acanthium* L. seeds. Pharmaceutical sciences 2014; 20(1): 6-11.
[61]. Móricz ÁM, Krüzselyi D, Alberti Á, Darcsi A, Horváth G, Csontos P, Béni S and Ott PG. Layer chromatography-bioassays directed screening and identification of antibacterial compounds from Scotch thistle. J Chromatogr A 2017;1524:266-272.
[62]. Molnár J, Szebeni GJ, Csupor-Löffler B, Hajdú Z, Szekeres T, Saiko P, Ocsovszki I, Puskás LG, Hohmann J and Zupkó I. Investigation of the antiproliferative properties of natural sesquiterpenes from *Artemisia asiatica* and *Onopordum acanthium* on HL-60 cells *in vitro*. Int J Mol Sci 2016;17(2):83.
[63]. Abusamra YA, Scuruchi M, Habibatni S, Maammeri Z, Benayache S, D'Ascola A, Avenoso A, Campo GM and Spina E. Evaluation of putative cytotoxic activity of crude extracts from *Onopordum acanthium* leaves and *Spartium junceum* flowers against the U-373 glioblastoma cell line. Pak J Pharm Sci 2015;28(4):1225-1232.
[64]. Csupor-Löffler B, Hajdú Z, Rethy B, Zupkó I, Máthé I, Rédei T, Falkay G and Hohmann J. Antiproliferative activity of Hungarian Asteraceae species against human cancer cell lines, Part II. Phytother Res 2009; 23:1109–1115.
[65]. Tehrani BE, Shahrestani R, Bahmani B, Mosaddegh M and Nader N. Cytotoxic activity of plants from Ardebil province. Research Journal of Pharmacognosy 2017; 4: 53.
[66]. Abuharfeil NM, Maraqa A and Von Kleist S. Augmentation of natural killer cell activity *in vitro* against tumor cells by wild plants from Jordan. J Ethnopharmacol 2000; 71: 55–63.
[67]. Shabsoug B, Khalil R and Abuharfeil N. Enhancement of natural killer cell activity *in vitro* against human tumor cells by some plants from Jordan. Journal of Immunotoxicology 2008; 5:279-285.
[68]. Sharifi N, Souri E, Ziai SA, Amin G, Amini M and Amanlou M. Isolation, identification and molecular docking studies of a new isolated compound, from *Onopordon acanthium*: a novel angiotensin converting enzyme (ACE) inhibitor. J Ethnopharmacol 2013;148(3):934-939.
[69]. Sharifi N, Souri E, Ziai SA, Amin G and Amanlou M. Discovery of new angiotensin converting enzyme (ACE) inhibitors from medicinal plants to treat hypertension using an *in vitro* assay. DARU Journal of Pharmaceutical Sciences 2013; 21:74-81.
[70]. Ghods R, Gharouni M, Amanlou M, Sharifi N, Ghobadi A and Amin G. Effect of *Onopordon acanthium* L. as add on antihypertensive therapy in patients with primary hypertension taking losartan: a pilot study. Adv Pharm Bull 2018; 8(1): 69-75.
[71]. Sharifi N, Souri E, Ziai SA, Amin G, Amini M and Amanlou M. Isolation, identification and molecular docking studies of a new isolated compound, from *Onopordon acanthium*: a novel angiotensin converting enzyme (ACE) inhibitor. J Ethnopharmacol 2013;148(3):934-939.
[72]. Angelov G, Georgieva S and Petkova-Parlapanska K. Antioxidant activity of extracts from cotton thistle (*Onopordon acanthium* L.). Science & Technologies 2012; 2(3): 19-23.
[73]. Hassanzadeh M, Sharifi N, Mahernia S, Rahimi N, Dehpour AR and Amanlou M. Effects of onopordia, a novel isolated compound from *Onopordon acanthium*, on pentylene tetrazole-induced seizures in mice: Possible involvement of nitric oxide pathway, Journal of Traditional and Complementary 2019; 30, https://doi.org/ 10.1016/j.jtcme.2019.11.005
[74]. Koochek MH, Ghochani A and Pipelzadeh MH. Effect of *Onopordon acanthium* on full-thickness dermal wound healing in rabbit. DARU J Pharm Sci 2000; 8: 45–49.

Ali Esmail Al-Snafi. "Constituents and pharmacology of Onopordum acanthium." *IOSR Journal of Pharmacy (IOSRPHR)*, 10(3), 2020, pp. 07-14.